CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

CIRM Comments on Draft NIH Guidelines for Human Stem Cell Research - 5/12/09

NIH Stem Cell Guidelines
MSC 7997
9000 Rockville Pike
Bethesda, Maryland, 20892-7997

The California Institute for Regenerative Medicine (CIRM) applauds NIH for its speed in issuing the above referenced Guidelines and welcomes the opportunity to respond. CIRM was established in 2004 when 59% of California voters agreed to support ethical embryonic and adult stem cell research. Included in this mandate is explicit authority to perform somatic cell nuclear transfer (SCNT), which is viewed as a potentially important approach for meeting CIRMs scientific mission and advancement of the field of regenerative medicine. With $3 billion in approved bond funds to be issued over 10 years, it is CIRM's mission to advance the ethical study of embryonic and adult stem cell research in order to improve the lives of patients. Additional information about CIRM may be found by visiting http://www.cirm.ca.gov/.

Like the NIH, CIRM is required to establish standards to ensure that its funded research is ethically responsible, scientifically worthy and is conducted with the interests of donors and patients. CIRM has supported efforts to develop and harmonize effective regulatory policy requirements to ensure ethically responsible research and to enable state, national and international collaboration and exchange.

Considerable analysis and input from stakeholders, including the scientific community went into formulating these comments. The process included the following activities:

- Policy review: Draft NIH guidelines were evaluated against the CIRM Medical and Ethical Standards regulations, national and international guidelines and policy.
- Key stakeholder interviews: CIRM staff interviewed researchers, program administrators and legal experts to identify priority issues.
- Impact analysis: Researchers, oversight committees and hESC providers were contacted to evaluate impact of the guidelines on material utilization and availability. The analysis included a survey of grantees (n=105) to characterize hESC utilization in disease-related CIRM-funded research.
- Survey national partners: CIRM staff participated in deliberations involving the Interstate Alliance on Stem Cell Research to identify interstate and international policy issues.
- Public Deliberation: A task force comprised of CIRM's governing board, the Independent Citizens' Oversight Committee ("ICOC") held a public hearing on May 7, 2009 to consider the guidelines and CIRM's response. The ICOC discussed and approved this response at a public meeting on May 12, 2009.

Summary of Major Recommendations:

CIRMs major recommendations are summarized in this section. Comments 1-6 constitute our priority recommendations for how the final NIH Guidelines can advance ethically responsible and scientifically worthy human stem cell research. Comments 7-8 relate to implementation considerations once final Guidelines are promulgated.

1. Recognize hESC lines derived in accordance with core principles for ethical responsibility. These core principles include:
   - Requiring rigorous independent oversight
   - Ensuring voluntary and informed donor consent
   - Requiring no undue inducements
2. Avoid disqualifying ethically responsible hESC lines or research projects through the retroactive application of detailed technical requirements.
3. Provide that verification of adherence to regulations and guidelines requiring ethically responsible donation can be established by:
   - For hESC lines derived from blastocysts donated in the U.S., approval by an Institutional Review Boards (IRBs) or equivalent such as an embryonic stem cell research oversight committee
   - For hESC lines derived from blastocysts donated outside the U.S., verification by aU.S. IRB or equivalent that procurement was consistent with the core principles of ethical responsibility
4. Explicitly deem all hESC lines derived from blastocysts donated prior to publication of the final NIH Guidlelines as conclusively eligible for NIH funding provided ethical standards in effect at the time of donation were satisfied, which shall be conclusively established by the prior approval of an IRB, or equivalent body, such as an embryonic stem cell research oversight committee.
5. Allow the use of hESC lines derived from eligible blastocysts[1] already deposited in tissue banks prior to the publication of the NIH guidelines provided there was IRB approval and oversight.
6. Permit the use of hESC lines derived through parthenogenesis provided they meet core standards for ethical responsibility.
7. Once final NIH Guidelines are promulgated, support registration and fund accreditation mechanisms to assure regulatory compliance and efficient use of research funding, including to:
   - Support and fund the development of a system to automatically register and identify hESC lines derived prior to publication of the final NIH Guidelines, provided an IRB or equivalent body such as an embryonic stem cell research oversight committee has previously deemed such lines as ethically derived.

[1] A *blastocyst* is a pre-implantation embryo that develops 5 days after the fertilization. The blastocyst is a mostly hollow sphere with an inner cell mass composed of 30-34 microscopic cells. These cells are referred to as *pluripotent* because they can differentiate into all of the cell types of the body. State, national and international laws and guidelines prohibit research on any blastocyst that has been *in virto* culture for longer than 14 days.

- Support and fund the development of a system to prospectively register new hESC lines derived after publication of the final Guidelines, provided such derivation satisfies requirements within the final Guidelines.
- Support and fund an accreditation mechanism for tissue banks that have established protocols consistent with the NIH draft Guidelines.

8. To reduce administrative burden, for those hESC lines that are listed on an NIH funded registry and /or are the subject of an IRB approval verifying ethical donation, no additional documentation requirements should exist above that which evidence such IRB approval and / or listing on such registry.

Discussion of Major Recommendations:

1. Recognize hESC lines derived in accordance with core principles for ethical responsibility.

Nationally and internationally, research is conducted in accordance with core principles for ethical responsibility. These principles emerged from the Nuremberg Code and have been adopted by leading nations, research institutions and professional bodies. These core principles include:

- Requiring independent oversight such as through IRBs which have extensive experience reviewing informed consent in the context of human tissue research;
- Ensuring a process for voluntary informed consent including the review of consent procedures performed outside the United States;
- Requiring no undue inducements to donors.

The federal Common Rule is embodied in Title 45 of the Code of Federal Regulations, which Institutional Review Boards (IRBs) are required to adhere to. Under these regulations IRBs must review and approve the process for obtaining voluntary informed consent from individuals participating in research – including the donation of cells and tissues (see Table 1).

Table 1: Consent Requirements Under U.S. Federal Law 45 CFR Part 46

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected duration of the subject's participation
- A description of the procedures to be followed
- Identification of any procedures which are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others which may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- For research involving more than minimal risk, an explanation as to whether any compensation is offered, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled

2. Avoid disqualifying ethically responsible hESC lines (vital for chronic disease research) or projects through the retroactive application of detailed technical requirements.

A fundamental concern is that established research materials that have already been deemed ethically derived and that are currently being used in NIH funded research could be disqualified by the retroactive application of technical requirements for procurement and consent. Potential research materials at risk include the Pre-2001 hESC lines, post-2001 hESC lines, and blastocysts stored in research tissue banks. The importance of these hESC lines for chronic disease research is illustrated in Table 2. The data are based on survey from 105 CIRM-funded researchers. Eighty-nine individual researchers reported using one or more hESC lines in disease-related research, which could ultimately improve the lives of patients suffering from a broad array of diseases.[2] Disqualification of such line on technical grounds could jeopardize established research programs in major disease areas. The table reflects actively funded research in the following disease areas:

- **Amyotrophic lateral sclerosis (Lou Gehrig's disease)**
- **Alzheimer's disease**
- **Huntington disease**
- **Parkinson's disease**
- **Injuries to the spine**
- **Heart disease & injury**
- **Hematopoietic ailments / blood disease (non-malignancy)**
- **Cancers (hematological, solid tumor)**
- **Fertility & reproductive health**
- **Foundational science including immunology**
- **Musculoskeletal/osteoarthritis**
- **Kidney disease**
- **Hearing impairment**
- **Balance impairment**

- **Avoid the retroactive application of detailed technical requirements. Any detailed requirements which are in addition to the standards that IRB's have been held to date (which standards include compliance with 45 CFR Part 46.116, National Academies' of Sciences Guidelines, and 2002 federal agency stem cell guidance) should be applied only prospectively to materials procured or derived after July 1, 2009.**

3. Provide that IRB approvals serve as the mechanism for verifying adherence to regulations and guidelines at the time of embryo / tissue donation and to establish that such research materials were ethically derived.

For hESC lines derived from blastocysts donated in the United States

Verification by an Institutional Review Board (IRB) of adherence to regulations and guidelines in place at the time of embryo donation should serve to establish that research materials were ethically derived. For lines derived in the United States prior

[2] Table 3 identifies the occurrence of use of specific stem cell lines by provider. Comments received by NIH from some providers suggest their materials will be disqualified by the retroactive imposition of technical requirements.

Table 2: hESC Utilization for Disease Research

hESC Utilization Reports Compiled by CIRM (n=89)

STEM CELL LINE	Neural & Neurodegenerative Ailments														
	ALS[1]	ALZ[2]	HD[3]	PD[4]	Spinal[5]	Other	Cardiac[6]	Blood[7]	Cancer[8]	Fertility[9]	Foundational Sci.[10]	HIV/AIDS	Diabetes	Musculoskeltal/Arth.[11]	Other[12]
BG01V, 01, 02, 03	X	X	X	X	X				X		X	X	X		
CyT49, CyT203													X		
ES lines (01 - 06)						X	X	X	X						
ESI-H3											X				
ESI017, 35, 49, 51, 53											X				
FES22, 29, 30, 61											X				
G7, W7, W10 (StemCellLife, CA)	X	X	X	X	X								X		
H1, H9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
H6, H7, H13, H14	X			X		X			X	X	X				X
HES2, 3, 4											X			X	
HSF1, HSF6				X				X	X	X				X	X
HuES lines (1-17)	X	X	X		X	X	X	X	X	X	X	X	X	X	X
I6	X	X	X	X	X								X		
iPS line A, line B											X				
Karolinska 181								X			X				
LLC-2P, 6P, 7P, 8P, 9P, 12PH, 15PH											X				
LSJ-1, LSJ-2		X				X		X						X	
MA01, 99								X			X				
Mel 1, 2, 3, 4				X			X	X	X		X	X			
MFS-5														X	
miz1, 4, 6											X				
SIVF0 01, 02, 03,05, 06, 07, 17HD, 18HD, 19, 20HD, 21, 22, 23											X				

105 responses were received by CIRM; 89 reported utilization of hESC lines; this table is based on the 89 reports

NOTE 1: This table only shows if a cell line is used in research for a particular disease/ailment/pathology. It does not refelct the numer of CIRM-funded Pis performing work in a particular field.

NOTE 2: *Tan color indicates most commonly reported stem cell lines used.*

1 Amyotrophic lateral sclerosis / Lou Gehrig's disease
2 Alzheimer's disease
3 Huntington disease
4 Parkinson's disease
5 Injuries to the spine
6 Heart disease & injury
7 Hematopoietic ailments / blood disease (non-malign
8 Cancers (hematological, solid tumor)
9 Fertility & reproductive helath
10 Foundational science including immunology
11 Musculoskeletal/osteoarthritis
12 Includes retinal, hearing/ balance, dental

Comments received by NIH from some cell line providers suggest many of the stem cell lines identified above will be disqualified from NIH-funded research through the retroactive application of detailed techinical requirements.

to the promulgation of the final NIH Guidelines, this determination would be based on adherence to the Common Rule. For lines derived after the promulgation of the final NIH Guidelines this determination would be based on adherence to the Common Rule and the additional requirements (if any) required by NIH Guidelines. Application of this system would enable utilization of all pre- and post-2001 lines derived in the U.S where there is IRB oversight and approval of the informed consent protocol.

Work with Pre-2001 lines should not be impaired by the additional technical requirements that provide limited value in ensuring ethical derivation yet could have the unintended result of interfering with the very research which was permitted before President Obama's Executive Order. Furthermore, Post-2001 lines made in the United States without federal funding but with a process to ensure ethical derivation, represent important building blocks for the field. To support continuity in research NIH should allow the continued use of materials obtained from donors in accordance with federal and state law at time of donation, including IRB approval of the donation protocol.

States such as California have developed research programs in accordance with the National Academies' of Sciences (NAS) Guidelines for Human Embryonic Stem Cell Research. These guidelines incorporate the federal Common Rule for review and oversight of human subjects research. In addition, state research programs incorporating the NAS Guidelines require an additional level of oversight by requiring review by a stem cell research oversight committee. This added oversight provides added assurance that research is ethically responsible, scientifically worthy, and conducted in accordance with applicable law.

Future lines derived in the United States from blastocysts procured after the promulgation of the final NIH Guidelines, could be required to conform to any additional requirements imposed by the NIH Guidelines.

- **CIRM has found that institutions can effectively assure through IRBs and/or embryonic stem cell research oversight committees (ESCROs) that post-2001 lines conform to the Common Rule and have been derived with IRB approval and oversight. Lines determined to adhere to regulations and guidelines at time of embryo donation should satisfy evidentiary requirements.**

For hESC lines derived from blastocysts donated outside the United States

Under the scheme recommended above, for hESC lines derived from blastocysts donated outside the United States by an IRB within the United States would determine, consistent with current practice, that there was acceptable review and oversight of the donation process[3]. An IRB's approval has been and will continue to

[3] In the case of donations taking place outside the United States, IRBs make a determination that a substantially equivalent oversight body reviewed the donation. A listing of listing of the laws,

be based on findings that, hESC derivation has been performed in accordance with core principles for ethical responsibility (see comment 1).

CIRM, so far, has performed an equivalency analysis for three nations, Canada, Japan and the United Kingdom. Each has developed policies and supporting regulatory regimes to ensure that research is ethically responsible, scientifically worthy, and conducted in accordance with internationally accepted norms of conduct. The hESC derivation performed under the Canadian Institutes for Health Research Guidelines, Japanese Guidelines for Derivation and Utilization of Human Embryonic Stem Cells and Human Fertilization and Embryology Authority license (UK) conform to national consensus standards for that jurisdiction and are acceptable for use in CIRM-funded research. These standards require ethical derivation including consent requirements deemed appropriate for the respective jurisdiction.

- **Given that international exchange and collaboration is imperative for the advancement of stem cell science, guidelines and regulations should allow IRBs to recognize the donation protocol for hESC lines derived outside the U.S.**

4. **Explicitly deem all hESC lines derived from blastocysts donated prior to publication of the final NIH Guidlelines as conclusively eligible for NIH funding provided ethical standards in effect at the time of donation were satisfied, which shall be conclusively established by the prior approval of an IRB, or equivalent body, such as an embryonic stem cell research oversight committee.**

   Work with lines already approved by an IRB or an equivalent body such as an embryonic stem cell research oversight committee prior to publication of the final NIH Guideline should not be impaired. The only means to protect millions of dollars in investment in programs already deemed consistent with ethical norms, is through explicit recognition of such lines as conclusively eligible for NIH funding without further review will. Applying additional technical requirements retroactively will serve little purpose in terms of ensuring ethical derivation, but it could have the unfortunate and unintended result of interfering with the very research which was permitted before President Obama's Executive Order. To date, CIRM has approved grants totaling over $761 million representing the largest source of funding for embryonic and pluripotent stem cell research in the world. A significant number of hESC lines utilized by CIRM grantees from 2001 through 2009 are pre-2001 / NIH-approved lines. The importance of these hESC lines for chronic disease research is illustrated in Table 2. A substantial research investment has been made by CIRM and others to develop and characterize many of these lines, which are often used as comparison (control) for evaluating newer lines. Table 3 illustrates the frequency a specific line utilized based on survey responses from 89 CIRM-funded researchers using hESC lines. A number of these lines are pre-2001; thus, they represent an

---

regulations, and guidelines that govern human subjects research in many countries around the world may be found at: http://www.hhs.gov/ohrp/international/HSPCompilation.pdf

important research foundation for the field. Limiting the use of such materials will slow the field and undermine the quality of the science.

- **Eliminate uncertainty and disruption of established research and explicitly authorize use of these cell lines.**

5. Allow the use of hESC lines derived from eligible blastocysts already deposited in tissue banks prior to the publication of the NIH guidelines provided there was IRB approval and oversight.

Nationwide there are a number of tissue banks that routinely collect blastocysts for research. These tissue banks are an important source of blastocysts for hESC derivation. Tissue banks adhere to detailed procedures for consenting donors and complying with state and national laws. Individuals and couples donating to these banks have gone through a very thoughtful and deliberative education and informed consent process. Direct experience with donors and research suggests that blastocysts are frequently donated out of an intense sense of altruism. Donors hope to contribute to humanity by supporting scientific discovery and medical research. NIH policy should not result in the exclusion of these materials from research if they were procured in an ethically responsible manner.

- **The NIH Guidelines should allow the use of hESC lines derived from blastocysts already deposited in tissue banks provided there was IRB approval and oversight of the donation process. Blastocysts subsequently donated to tissue banks should conform to the current NIH standard.**

Table 3: Self-Reported Use of Selected hESC Lines from CIRM-funded Researchers

	Cell Line	Date Created	Occurrence
WiCell	H1	1998	47
	H7	1998	16
	H9	1998	61
	H13	1998	3
	H14	1998	4
UCSF	HSF1	2001	11
	HSF6	2001	16
Melton / Harvard	HuES-1	2004	3
	HuES-2	2004	3
	HuES-3	2004	1
	HuES-6	2004	3
	HuES-7	2004	4
	HuES-8	2004	4
	HuES-9	2004	10
	HuES-10	2004	2
	HuES-11	2004	3
	HuES-12	2004	3
	HuES-13	2004	1
	HuES-14	2004	1
	HuES-15	2004	3
	HuES-17	2004	2
	HES 2	2000	3
	HES 3	2000	4
Pera	LSJ-1	2006	3
	LSJ-2	2006	4
Belmonte	ES01	2007	2
	ES02	2007	3
	ES03	2007	4
	ES04	2007	4
	ES05	2007	1
	ES06	2007	1
	MEL 1,2,3,4		3
BresaGen	BG01	2001	9
	BG01V	2001	4
	BG02	2001	4
	BG03	2001	4

6. **Permit the use of hESC lines derived through parthenogenesis provided they meet core standards for ethical responsibility.**

   Established parthenogenetic cell lines represent an important scientific resource due to their unique genetic constitution and method of derivation. Research involving the comparison of embryo derived lines, induced pluripotent lines from somatic cells, and parthenogentic lines may be particularly informative for understanding a range of issues related to mechanisms of reprogramming and differentiation. In addition, the unique immunologic profile of parthenogenetic lines may be particularly important in the development of cell products for clinical transplantation.

   - **NIH should allow the use of parthenogentic lines provided materials were procured in accordance with federal and state law at time of donation, including IRB approval of the donation protocol. Lines derived subsequently should conform to the current NIH standard.**

7. **Once final NIH Guidelines are promulgated, support mechanisms to assure regulatory compliance and efficient use of research funding, including:**

   - **Support and fund the development of a system to automatically register and identify hESC lines derived from blactocysts donated prior to publication of the final NIH Guidelines, provided an IRB or equivalent body such as an embryonic stem cell research oversight committee has previously deemed such lines/donations as ethically derived.**

     In 2006 CIRM adopted regulations requiring research institutions to determine that hESC lines utilized in sponsored research conform to specific consent and oversight requirements. Consistent with the proposed draft NIH guidelines, CIRM requires institutions to assure hESC lines comply with these regulatory requirements.

     In 2007, CIRM implemented a regulatory evaluation. Twenty-one research institutions participated in workshops designed to discuss the impact of CIRM regulations on research practice (see http://www.cirm.ca.gov/meetings/pdf/2007/050907_item_8b.pdf). Participant institutions reported the continued evaluation of hESC provenance represented the major resource commitment for oversight committees. It was common for multiple institutions to be evaluating the same lines resulting in a duplication of labor. Consequently, CIRM determined that there was need for a registry system to serve as a single point for verification.[4]

[4] To address this need, CIRM supports the International Society for Stem Cell Research effort to develop provenance registry. This registry is designed to support a determination that specific cell lines conform to regulatory requirements. The registry is being developed by ISSCR, and CIRM is committed to supporting the acquisition of provenance information. CIRM believes this approach, involving registry development by an external and independent scientific organization is an effective approach.

Further, as illustrated by tables 2 and 3, numerous hESC lines have made a substantial contribution to disease-related research. Most lines have been reviewed and approved for research use under state regulatory requirements that conform to the National Academies' of Sciences Guidelines including review by an embryonic stem cell research oversight committee. To support proposed and ongoing research, hESC lines approved under state regulation or contracts that conform to the NAS Guidelines, should be immediately registered as compliant provided they were derived from human embryos that were created for reproductive purposes.[5]

- **To support more efficient use of research funds, consistency and better certainty among NIH grantees, NIH should support initiatives designed to determine the compliance status of established hESC lines. The compliance status of hESC lines should be available to funded researchers through a registry or database.**

- **Support and fund the development of a system to prospectively register new hESC lines derived after publication of the final NIH Guidelines, provided such derivation satisfies requirements within the final Guidelines.**

The derivation stage represents an opportune time to compile information related to donor consent and other aspects of blastocyst procurement. CIRM and the Interstate Alliance on Stem Cell Research (IASCR) have developed a proposed registration mechanism that includes certification by an independent review body. This mechanism leverages established review and oversight procedures to provide assurance that research is ethically responsible, scientifically worthy, and conducted in accordance with applicable law. The registration form includes a certification that informed consent for the blastocyst donation conforms to the *National Academies' Guidelines for Human Embryonic Stem Cell Research* (NAS Guidelines) and the status of donor payments.

- **NIH should support this assurance mechanism by encouraging oversight bodies to certify newly derived lines conform to requirements for ethical derivation.**

- **Support and fund a voluntary mechanism for identifying tissue banks that have established protocols consistent with the NIH draft Guidelines.**

Tissue banks are an important source of blastocysts for hESC derivation. Tissue banks adhere to detailed procedures for consenting donors and complying with state and national laws. NIH should consider a voluntary mechanism for

[5] For example, registering lines already approved under state programs will immediately make materials available for research funded under the federal the American Recovery and Reinvestment Act (the Stimulus Program).

identifying tissue banks that implement procedures and policies consistent with the final NIH Guidelines. Such a system could provide assurance to donors and researchers regarding the banks commitment to ethically responsible research.

- **NIH should consider for a voluntary mechanism for identifying compliant tissue banks.**

8. **To reduce administrative burden for those hESC lines that are listed on a NIH funded registry and / or are the subject of an IRB approval verifying ethical donation, no additional documentation requirements exist above that which evidences such IRB approval and / or listing on such registry.**

   The draft Guideline imposes extensive documentation requirements to establish a number of requirements. These include, documentation that at the time of donation "decisions related to the creation of human embryos for reproduction purposes were made free from influence of researchers," and that "there was a clear separation between the prospective donor(s)'s decision to create human embryos for reproductive purposes and the prospective donor(s)'s decision to donate human embryos for research purposes." Establishing these two criteria in particular may require a review of an institution's procedure's and practices – in essence an audit which could be time consuming. Rather than mandating research institutions to independently duplicate such a review and maintain documentation of such, allowing research institutions to rely on the prior verification by a registry or an IRB that has already conducted such a review would be far more efficient and serve the purpose of ensuring ethical donation.